Molecular machines

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MOLECULAR MACHINES

Springing into action

Controlling the movements of molecular systems through external stimuli is crucial for the construction of nanoscale mechanical machines. A spring-like compound has now been prepared — a double helicate that retains its handedness under ion-triggered extension and contraction.

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Virtually every biological process, from intracellular transport to muscle contraction, is driven by a molecular machine. These biological machines carry out pretty much the same functions as the macroscopic ones, but they take very different forms. Whereas macroscopic machines typically operate under the constraints of friction, inertia and gravity, their biological counterparts operate in the nanoworld against the Brownian storms created by the random movements of molecules in solution[1].

The apparent ease with which biological machines operate fascinates and inspires scientists, while at the same time challenging us to learn how to construct compounds that can perform mechanical functions[2,3]. A variety of ingenious systems have been prepared, including molecular muscles, motors and shuttles[4–6] — but it remains notoriously difficult to control these movements and translate them from the nanoscale into a macroscopic motion. In particular, despite its ubiquity in biological systems, mimicking spring-like function at the nanoscale has proven highly challenging. Writing in *Nature Chemistry*, Yoshio Furusho and co-workers now describe[7] a molecular double helix that behaves in a similar manner to a macroscopic spring — that is, undergoes contraction and extension while winding and unwinding in a unidirectional sense.

Ion binding and release processes are key mechanisms in biological machines. The functioning of some muscle tissue, for example, relies on calcium ions binding. The interaction between the muscle components myosin and actin is governed by the calcium-sensing complex troponin C, which activates or inhibits muscle contraction through calcium binding and release. Taking a leaf out of nature's book, Furusho and co-workers have used ion-binding events to trigger the spring-like motion of a helicate — a motif that is also omnipresent in nature, the best known being the DNA double helix.

The researchers had previously constructed a double-stranded helicate[8] consisting of two hexaphenol strands bridged by two boron atoms through the formation of two spiroborate ($-BO_4$) moieties, and accommodating a sodium cation in its central position. The sodium ion was coordinated to eight oxygen atoms — the two central hydroxyl groups of each hexaphenol strand and the two closest oxygen atoms of each spiroborate moiety. Furusho and colleagues noticed, however, that the four central hydroxyl groups weren't necessary to hold the complex together and replaced them with hydrogen atoms, thus preparing a new double helicate in which the central sodium cation is coordinated only to the spiroborate moieties (shown in Fig. 1).

The inclusion and removal of the central sodium ion triggers the contraction and extension of the helix. As a sodium ion binds to the spiroborate moieties, it shields the electrostatic repulsion within the helix's core, causing its contraction along its long axis. When cryptands are added to the solution, they bind to the sodium ions, removing them from the double-helicate complex. This unmasks the negative charges between the spiroborate moieties, causing them to repel each other and resulting in the partial unwinding of the helix. A detailed analysis of the structure by X-ray crystallography and nuclear magnetic resonance reveals that the helix approximately doubled its length, from 6 to 13 Å (Fig. 1).

In macroscopic and biological springs, the contraction and expansion of springs is typically accompanied with unidirectional twisting, but this has rarely been observed in synthetic molecular systems. Typically, on contraction or extension, synthetic helicates adopt a non-helical conformation, which leads to a racemization of the helicate and a twisting in both the right- and left-handed directions. The double helicate described here, however, retained its inherent chirality; circular dichroism studies show that extension by unwinding of the double-stranded helix proceeds clockwise, and contraction by winding proceeds anticlockwise.

The spring-like motion can be repeated many times simply by adding sodium ions or cryptands (which equates to removing sodium ions) to the solution. The rate of the extension process is slower than that

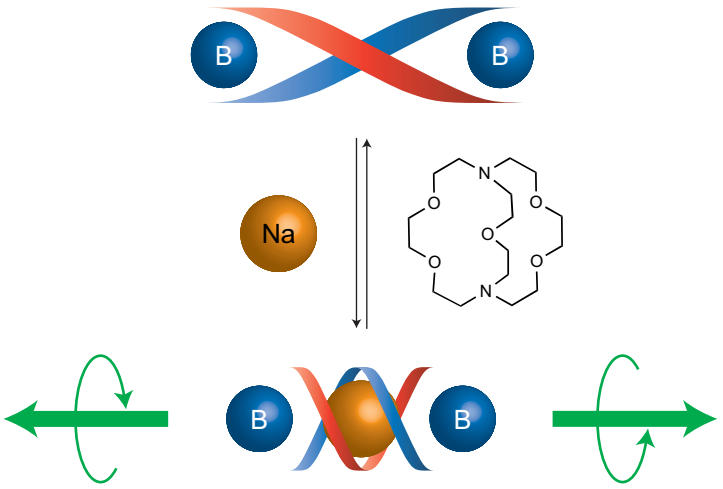

Figure 1 | Spring-like molecular motion. Inclusion and removal (through trapping by a cryptand) of a sodium ion triggers the contraction and extension of a double helicate. These events are accompanied by a unidirectional twisting.

of the contraction one — a feature that is attributed to the differences between the sodium binding processes involved (sodium–helicate and sodium–cryptand).

This elegant system shows how a clever design taking advantage of the unique features of helices can lead to a spring-like mechanical motion at the nanoscale. The next step could be an autonomous spring-like motion, in which the metal ion would bind successively to different helical strands. Making the leap to translating the molecular systems operation to macroscopic movement[9], reminiscent of the actin–myosin system that achieves muscle contraction, will be a challenge. Any such system will necessitate binding an ensemble of molecular springs to a surface and achieving concerted action. One could also foresee associating the ion binding and release events to a catalytic function, or controlling it by light irradiation. This would set the stage for the construction of a truly molecular mechanical device.

The molecular spring presented by Furusho and co-workers[7] combines the beauty of molecular helicity with a useful function and is a significant step on the long and winding road towards molecular nanotechnological devices. ❐

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REACTION KINETICS

Catalysis without a catalyst

Can two identical reactors with the same concentrations, under identical physical conditions, have reaction rates that differ by a factor of a thousand? A study now shows that, although not true in uncrowded environments, a reactant's starting point makes a large difference to reaction kinetics in identically crowded systems, such as cellular nuclei.

Raoul Kopelman

For a reaction to have superfast kinetics, compared with expectations from textbook equations, it helps if a higher power intervenes and microscopically arranges the reacting molecules to be close to each other — closer than in a random distribution. Such 'non-classical' kinetics do occur for some heterogeneous chemical reactions and may play a large role in biology. Writing in *Nature Chemistry*, Olivier Bénichou and colleagues use theory to investigate such "geometrically controlled reactions"[1]. They study reactions in a geometrically confined (topologically tortuous) reaction space in which the reactants have a spatially ordered distribution (Fig. 1). Such situations are of much interest at present because they may be typical of highly significant subcellular biochemical reactions of potential biomedical importance, such as gene transcription. Similar situations are also encountered in condensed-state physical and chemical reactions, such as exciton and electron–hole recombination or trapping, which have relevance to photonics and solar-energy science.

Bénichou and colleagues[1] use theory that goes beyond what has been generally termed non-classical or fractal-like kinetics, but still use a random-walk-based approach (that is, diffusion-limited reaction kinetics) to obtain analytical expressions that allow straightforward computations. To understand such theory we must first introduce the classical concepts of chemical reaction kinetics, where an elementary bimolecular reaction, at time t, is described by $R(t) = kA(t)B(t)$. Here, $A(t)$ is the instantaneous concentration (or activity) of reactant A, and $B(t)$ is that of reactant B. $R(t)$ is the instantaneous reaction rate and k is a constant that doesn't change with time and depends on the transport coefficients of the reactant molecules, as well as on the so-called reaction cross-section, or reaction probability at collision. What this classical formula does not seem to depend on is the size and shape of the reaction vessel, or the locations of the molecules. What is assumed implicitly in this expression is that the chemistry is taking place within a large reaction vessel with a homogeneous and random distribution of molecules at all times, that is, with perfect stirring. Furthermore, it is implicit that the so-called exploration volume, $V(t)$, which is the volume that a reactant visits in a given period of time, increases (at least) linearly with time. As soon as any of these idealized conditions is relaxed, the equation above has to be modified. For instance, without perfect stirring, k becomes a time-dependent quantity, that is, $k(t)$, which has a monotonically descending dependence on time[2].

To understand this better, let's describe the distinction between diffusion in one-dimensional and three-dimensional (3D) exploration spaces with the following analogies: (1) 'the drunk in an alley always returns to the bar'; (2) 'the drunk space pilot hardly ever manages to return to the bar planet'. Implicit in the above analogies is that the drunk performs a diffusive (random) walk along the alley, and likewise, the pilot randomly changes the direction of flight, that is, performs a random walk in 3D space.

Mathematics teaches us that, in one dimension, $V(t)$ increases (asymptotically) as $t^{1/2}$ (even if the alley is infinitely long), whereas in three dimensions it increases linearly with t. Two equivalent ways of looking at that[3] are: in one dimension (even if infinitely long, and in infinite time) the probability of the drunk (random walker) returning to the bar (origin) is unity, and thus his 'escape probability' is zero; however, the probability of the drunk space pilot returning to the bar planet is far from unity, for the drunk pilot manoeuvres in three dimensions, and thus his escape probability is finite. The above considerations distinguish